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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,525	11/29/2001	Erlinda M. Gordon	EPE1110-1	6086

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EXAMINER	
SHUKLA, RAM R	

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,525	GORDON ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *6 and 11-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of the invention of group I, claims 1-5 and 7-10 in Paper No. 12 is acknowledged.

2. Claims 1-22 are pending.

3. Claims 6 and 11-22 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

4. Claims 1-5 and 7-10 are under consideration.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising the vector of claim 1 wherein said composition is directly administered to a tumor in an animal, does not reasonably provide enablement for any method of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claimed invention encompasses delivering a targeted retroviral vector to any tissue and treat any disease or cancer by administering the vector by a method. The specification as filed is not enabling for the invention commensurate with the full scope of the claims because the art of targeting a therapeutic gene to any tissue using any retroviral vector is unpredictable as has been recognized by arts of skill and therefore would require undue experimentation.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242). Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Anderson (Nature 392(supp):25-30, 1998) also discusses problems associated with retroviral vector, such as level of express, choice promoters, production of particles

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at a level sufficient for pharmaceutical application etc. (see the right column on page 26). More recently, Hu and Pathak (Pharmacology Reviews 52:493-511, 2000) indicated that while retroviral mediated gene therapy was effective in gene therapy, many improvements are needed and that it is unlikely that one system will be the best tool for gene therapy of all the diseases (see section on future directions on page 508 in the left and right columns). While applicants' specification supports efficient transfer for *ex vivo* and *in vivo* direct injection of a targeted vector in a tumor, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any mode of delivery. The specification fails to teach any specific targeting techniques that will target the vector to any tissues or cell, fails to provide any working examples which encompass vector targeting to any tissue, and fails to direct the skilled artisan to teachings in the art that teach targeting strategies that will target a retrovial vector with modified surface to any tissue or cell, which would allow one of skill in the art to practice the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-5 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hall et al (WO 98/44938, 15 October 1998).

This art teaches a retroviral particle wherein the viral surface protein has been modified to include a targeting polypeptide that binds to an extracellular

matrix component of a cell and the particle also comprises a therapeutic gene. The extracellular component of the cell may be a collagen and the binding domain may be a collagen-binding domain such as present in Von Willebrand collagen factor (see the description on page 7). The therapeutic gene present in the vector can be any gene, such as a cytokine, including GM-CSF. The art also teaches method of delivering therapeutic genes to tumor and a method of treatment (see the entire disclosure including that on pages 7, 15, 20-22, examples, and claims, for example, claims 17, 18).

Therefore, Hall et al anticipates the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-5 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hall et al[1] (W0 98/44938, 10-15-1998) or Hall et al[2] (Human Gene Therapy 11:983-993, 2000) or Liu et al (Journal of Virology 74:5320-5328, 2000) or Gordon et al (Cancer Research 60:3343-3347, 2000) in view of Kurane et al (Annals of Surgery 4:579-585, 1997) and Borrello et al (Human Gene Therapy 10:1983-1991, 1999).

Hall et al[1] teaches a retroviral particle wherein the viral surface protein has been modified to include a targeting polypeptide that binds to an extracellular matrix component of a cell and the particle also comprises a therapeutic gene. The extracellular component of the cell may be a collagen and the binding domain may be a collagen-binding domain such as present in Von Willebrand collagen factor (see the description on page 7). The therapeutic gene present in the vector can be

any gene, such as a cytokine, including GM-CSF. The art also teaches method of delivering therapeutic genes to tumor and a method of treatment (see the entire disclosure including that on pages 7, 15, 20-22, examples, and claims, for example, claims 17, 18).

Hall et al[2], Lieu et al and Gordon et al teach retroviral vectors that can target a retroviral vector to extracellular matrix (see the entire documents). These articles also teach that these vectors can be used for targeted delivery of therapeutic agents to tumor or tumor associated vasculature (see the abstracts and rest of the articles). These articles do not teach a targeted vector comprising a cytokine or GM-CSF sequence.

Kurane et al and Borrello et al teach use of cytokines as adjuvant to tumor vaccines and that GM-CSF or other cytokines when delivered to tumors produced anti-tumor effects (see the entire documents).

At the time of the invention, it would have been obvious to an artisan of skill to modify the vector(s) of Hall et al, Liu et al or Gordon et al by cloning the GM-CSF encoding sequences taught by Borrello et al with a reasonable expectation of success and use the resultant vector for delivering GM-CSF to a tumor in an animal. An artisan would have been motivated to make such a vector because Borrello et all and Khurane et al teach that GM-CSF elicits antitumor effects and because the retroviral vectors of Hall et al, Liu et al and Gordon et al were designed for targeted delivery of therapeutic genes to tumors.

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this

application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632